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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/758,772	GUNZBURG ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *16 and 18-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5-10-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of group I, claims 1-15 and 17, in the reply filed on 5-10-06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 16 and 18-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5-10-06.

Claims 1-40 are pending. Claims 1-15 and 17 are under consideration.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-15 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "WAP" in claims 1 and 13 is vague and renders the claims indefinite. The term "WAP" is an abbreviation that can stand for various meanings. It is unclear what it stands for. Spelling out the term "WAP" would be remedial. Claims 2-12 and 15 depend from claim 1. Claims 14 and 17 depend from claim 13.

The term "MMTV" in claims 1 and 13 is vague and renders the claims indefinite. The term "MMTV" is an abbreviation that can stand for various meanings. It is unclear

what it stands for. Spelling out the term "MMTV" would be remedial. Claims 2-12 and 15 depend from claim 1. Claims 14 and 17 depend from claim 13.

The phrase "select from the group consisting of genes which codes for proteins such as Herpes Simplex Virus thymidine kinase gene ... **or** cytokines such as IL-2" in claim 11 is vague and renders the claim indefinite. It is unclear what genes are included in the group. Changing the term "or" to "and" would be remedial.

5. Regarding claim 11, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

6. Claim 1 recites the limitation "the WAP or MMTV regulatory sequences" in line 2. There is insufficient antecedent basis for this limitation in the claim.

7. Claim 13 recites the limitation "the WAP or MMTV regulatory sequences" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-15 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for construction of vectors pMMTV-BAG and pWAP-BAG containing β-galactosidase gene under the control of MMTV and WAP, respectively, and the expression of β-galactosidase in explanted normal primary human mammary tissue infected with virus containing said vectors set forth above, does not

reasonably provide enablement for any DNA construct or a recombinant viral vector comprising any therapeutic gene under the control of a MMTV promoter or a WAP promoter and said therapeutic gene is expressed in a cell *in vivo* for the treatment of disorders or diseases of human mammary cells, a retrovirus particle comprising said construct, a cell line comprising said construct, and a human cell comprising a retroviral provirus expressing any therapeutic gene under the control of a MMTV promoter or a WAP promoter for the treatment of disorders or diseases of human mammary cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a DNA construct or a recombinant viral vector, such as a retroviral vector, comprising at least one therapeutic gene under the control of a MMTV promoter or a WAP promoter for the treatment of disorders or diseases of human mammary cells including human mammary carcinoma, a recombinant retroviral particle produced by culturing a packaging cell line harboring said retroviral vector, a retroviral provirus carrying a construct comprising at least one therapeutic gene under the control of a WAP or MMTV regulatory sequence integrated in the human genome, a cell line containing said construct, and a human cell containing said retroviral provirus.

The claims read on expression of a therapeutic gene *in vitro or in vivo*. The claims also read on the use of the DNA construct, the retroviral vector, the retroviral particle or provirus containing said retroviral vector set forth above, a cell line containing said DNA construct, or a human cell containing said retroviral provirus for gene therapy *in vivo*, e.g. the treatment of disorders or diseases of human mammary cells including human

mammary carcinoma, in light of the specification (e.g. p. 2-7). A human cell containing a retroviral provirus encompasses any human cell that is transduced with a rectrovirus in vivo, therefore, it reads on gene therapy in vivo.

The specification of the instant invention discloses the construction of vectors pMMTV-BAG and pWAP-BAG containing β-galactosidase gene under the control of MMTV and WAP, respectively. The specification shows the expression of β-galactosidase in explanted normal primary human mammary tissue infected with virus containing said vectors set forth above.

It was well known in the art that β-galactosidase is a molecular marker. The expression of a β-galactosidase in explanted normal primary human mammary tissue infected with vectors pMMTV-BAG and pWAP-BAG is not considered to enable any therapeutic gene expression under the control of a MMTV promoter or a WAP promoter for gene therapy in vivo, such as treating disorders or diseases of human mammary cells including human mammary carcinoma, since expression of a marker gene can not be extrapolated into expression of any therapeutic gene *in vivo* such that said expression provides therapeutic effect for a gene therapy. The specification fails to provide evidence that expression of a marker gene relates in any way to successful expression of other genes for providing therapeutic effect for gene therapy *in vivo*.

The specification fails to provide adequate guidance and evidence that the use of a DNA construct or a cell line containing said DNA construct expressing a β-gal or any therapeutic gene product under the control of a WAP or a MMTV regulatory sequence *in vivo* would provide sufficient expression of said β-gal or said therapeutic gene product for a duration of sufficient time to effect therapeutic effects for a particular disease or

disorder, such as disorders or diseases of human mammary cell *in vivo*. The specification fails to provide adequate guidance and evidence for the use of a retroviral particle or a retroviral provirus expressing any therapeutic gene under the control of any MMTV promoter or any WAP promoter in vivo would provide sufficient expression of said therapeutic gene product for a duration of sufficient time to effect therapeutic effects for a particular disease or disorder, such as disorders or diseases of human mammary cell *in vivo*.

The nature of the invention being gene therapy, the state of the prior art was not well developed and is highly unpredictable. Verma (Sept. 1997, Nature, Vol. 389, pages 239-242, IDS-21) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and points out that "among the

design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101, IDS-22) reports that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy *in vivo*. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (e,g, bridging pages 81-82).

In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198, IDS-27) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). The specification only shows the expression of beta-galactosidase in explanted normal primary human mammary tissue infected with retrovirus containing the vectors set forth above but fails to teach one skilled in the art how to deliver the DNA construct, the retroviral particle, the retroviral provirus, or the cell line containing said DNA construct to a subject via various administration routes

such that it reaches targeted cells and provide sufficient expression of gene product so as to effect a therapeutic response to any particular disease or disorder *in vivo*.

The specification also fails to provide adequate guidance and evidence for whether any WAP promoter derived from any organism other than mouse can direct gene expression in human mammary cells or any other human cells, and whether a MMTV promoter can direct gene expression in any human cell type other than human mammary gland cells. The specification points out "One regulatory element demonstrated to give rise to expression in the pregnant and lactating mouse mammary gland is a small region of the rodent WAP promoter. It is therefore not predictable that this regulatory element will function at all to direct expression in human mammary cells and/or allow expression in human mammary carcinoma cells" (specification, page 2, lines 15-25). The mechanisms of stimulating downstream gene expression via various WAP promoters derived from different organisms may vary because the difference of the core elements of WAP promoters and the cellular interacting transcriptional factors in the cells may vary from species to species. Therefore, it would be unpredictable whether any WAP promoter other than the mouse WAP promoter will direct gene expression in human mammary cells or any other human cells. It is noted that claims 2 and 3 specify the regulatory sequence comprises the proximal 445 bp of the WAP promoter and the 320 bp XhoI/XbaI fragment of the WAP promoter region, respectively. Since the claims encompass using various WAP promoter sequence derived from various organisms, the WAP promoter sequence and its core element could vary among different species and it is unclear whether the proximal 445 bp region or the 320 bp XhoI/XbaI fragment of the various WAP promoters would have the same gene expression stimulating activity as that

of the mouse WAP promoter disclosed in the instant invention. The specification fails to provide an enabling disclosure for the use of various WAP promoter sequences for expression of at least one therapeutic gene so as to provide therapeutic effect in the treatment of disorders or diseases of human mammary cells in vivo.

Different cell types may have different mechanisms in the transcriptional control of gene expression and the transcriptional machinery in different cell type could differ. Thus, gene expression via a MMTV promoter in normal human mammary gland cells or human bladder carcinoma cells does not necessarily imply that the MMTV promoter can direct gene expression in other human cell types. Further, the MMTV promoter is known in the art to be a mammary cell-specific promoter, it is likely that the MMTV promoter can not direct gene expression in any human cell type other than mammary cells.

In view of the lack of guidance and evidence on whether any WAP promoter other than mouse mammary WAP promoter could direct gene expression in human mammary cells or in human mammary carcinoma cells, on whether a MMTV promoter can direct gene expression in any human cell type other than human mammary gland cells, the unpredictable nature of gene therapy in vivo, and the unpredictable nature of a WAP promoter or a MMTV promoter in directing gene expression in different cell types for gene therapy *in vivo*, it would have required a skilled person in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of skill which is high, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1, 6-8, 10-13, 15 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Barber et al., 2001 (US patent No. 6,241,982).

The claims are directed to a DNA construct or a recombinant vector, such as a retroviral vector, comprising at least one therapeutic gene, such as a cytosine deaminase gene or a cytokine gene, under the control of a WAP regulatory sequence, a recombinant retroviral particle or provirus comprising said retroviral vector, a cell line harboring said retroviral vector, and a human cell containing a retroviral provirus.

Barber teaches preparation of a recombinant retroviral vector or retrovirus expressing a cytotoxic gene, such as a cytosine deaminase gene, under the control of WAP promoter, production of vector particle by using packaging cell lines, introduction of the retroviral vector into human cells (e.g. abstract, column 4, 5, 14, 20, 35, 36). It is inherent that introduction of retroviral vector into human cells will result in retroviral provirus in said human cells. Thus, claims 1, 6-8, 10-13, 15 and 17 are anticipated by Barber.

It should be noted that claims 1, 6-8, 10-13, 15 and 17 are product claims. The elements encompassed in the claimed retroviral vector are at least one therapeutic gene and the WAP regulatory sequence. The intended use of the DNA construct, retroviral vector, retroviral provirus, or the cell line containing said DNA construct for the treatment of disorders or diseases of human mammary cells is irrelevant for 102 rejection.

12. Claims 1-3 and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Ebert et al., 1991 (Biotechnology, Vol. 9, p. 835-838).

Claims 1-3 and 6-8 are directed to a DNA construct or a recombinant vector comprising at least one therapeutic gene under the control of a WAP regulatory sequence, such as the proximal 445 bp of the WAP promoter and the 320 bp XhoI/XbaI fragment of the WAP promoter region.

Ebert teaches preparation of a plasmid expression vector containing the murine whey acid protein (WAP) promoter operably linked to a cDNA encoding a modified version of human tPA (e.g. abstract). The WAP promoter contains a 2.6 kb EcoRI-KpnI fragment upstream of the murine WAP gene (e.g. p. 835, right column) and said 2.6 kb fragment includes the proximal 445 bp of the WAP promoter and the 320 bp XhoI/XbaI fragment of the WAP promoter region. The human tPA gene is considered a therapeutic gene. Thus, claims 1-3 and 6-8 are anticipated by Ebert.

13. Claims 1 and 4-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Habraken et al., 1993 (Mutation Research, Vol. 293, No. 3, pp. 187-195).

Claims 1 and 4-8 are directed to a DNA construct or a recombinant vector comprising at least one therapeutic gene under the control of a MMTV regulatory sequence, such as the U3 region of MMTV and the 0.6 Kb PstI MMTV promoter fragment.

Habraken teches preparation of pMSG expression vector containing a coding sequence encoding either E. coli AlkA gene or rat APDG cDNA under the control of the MMTV-LTR promoter. The E. coli AlkA gene or rat APDG gene is considered a therapeutic gene. The MMTV-LTR promoter inherently includes the U3 region or the 0.6 Kb PstI MMTV promoter fragment. Thus, claims 1 and 4-8 are anticipated by Habraken.

14. Claims 1 and 4-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Salmons et al., 1985 (Virology, Vol. 144, p. 101-114).

Claims 1 and 4-8 are directed to a DNA construct or a recombinant vector comprising at least one therapeutic gene under the control of a MMTV regulatory sequence, such as the U3 region of MMTV and the 0.6 Kb PstI MMTV promoter fragment.

Salmons teaches preparation of a hubrid endogenous-exogenous MMTV provirus pGR102 containing the 5' LTR-gag of GR40 and the pol-env-3' LTR of the exogenous provirus and upon transfection into feline kidney cells, the hybrid provirus directed the synthesis of gan and env proteins (e.g. abstract). The MMTV LTR promoter inherently include the U3 region and the 0.6 Kb PstI MMTV promoter fragment (see Figure 1). The

env or gag gene is considered a therapeutic gene. Thus, claims 1 and 4-8 are anticipated by Salmons.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER